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"Gene-Environment Interactions as the New Research Model in Environmental Health"

Thank you very much for inviting me to discuss the influence of environment on human health.

The goals of environmental health research are establishing and maintaining a healthy, livable environment for humans and other species and promoting an environment that improves well-being and all aspects of mental and physical health. This environment must be sustained into the future and be a setting in which population growth, manufacturing, and agriculture can thrive.

We all recognize that many important achievements have helped create a cleaner, healthier environment, and our past research strategies have allowed many successes in understanding mechanisms of environmentally linked diseases.

To continue making strides in the future, we will need to focus on the interplay of genes and environment. It is the interplay – "gene-environment interactions" – that holds the greatest promise in the fight to prevent and control environmentally related diseases, including cancer and many other chronic diseases. This is the main point I wish to make today.

There are two recent advances in the fields of human genetics and environmental health that will define our research in the future.

First, we now have the sequence of the human genome in hand and are beginning to understand the individual-to-individual variations that modify susceptibility to disease.

Second, we are now working with an expanded definition, or view, of environmental exposures, that includes diet, lifestyle, socio-economic status and other factors, including environmental pollutants. This expanded view of environmental factors will allow us to conduct more meaningful studies of environmental contributors to disease.

The research model of understanding a relatively rare but strong disease gene or a strong environmental toxicant has served us very well in the past in defining the molecular biology of disease, and in prevention. However, this model will not be sufficient to address the more common diseases in the future, since only a small percentage of disease can be attributed to the rare dominant disease genes or to high levels of strong toxicants. Instead, new science and a new scientific toolbox will be needed, along with more research involving the common genes that modify an individual's response to environmental factors. Fortunately, the genomics era will provide us with this new toolbox, and along with the expanded view of environmental factors, the field of environmental health research has an exciting, new opportunity.

I will now very briefly describe some of the work pointing to the role of environment in disease and how understanding gene-environment interactions will improve our ability to prevent disease.

The past few years have seen a number of studies that illustrate the importance of environment. For example, by comparing disease rates in twins, scientists have managed to tease apart the relative contributions of genes and environment. We now know that environment accounts for over 50% of cancer risk depending on the site of the cancer. Twin studies on Parkinson's Disease reveal that environment accounts for 85% of the risk in the late-onset cases of this disease. For autoimmune diseases such as MS (multiple sclerosis) and Lou Gehrig's Disease, environmental factors account for 60% to 75% of disease risk.

Environment, indeed, is a major determinant of risk for a broad range of diseases. Environment, however, is not the total answer in disease development. Two people with the same exposure can have very different outcomes. Differences in susceptibility appear to be due to variations in genes coding for proteins critical in the body's response to environmental stress. These proteins include metabolizing enzymes, DNA repair enzymes (as we have heard this morning from Dr. Winn), signaling molecules, and receptors, among others. Someone inheriting a gene that produces a weak or ineffective form of one of these proteins will be more susceptible than a second person inheriting a gene that makes a more effective protein. This is because the first person might be less able to break down, or handle, a toxicant or to repair the specific cellular damage caused by the toxicant. Thus, understanding the <u>combination</u> of "modifier genes" and specific environmental exposures is critical toward defining the causes of disease. Neither acts alone. It is the two interacting, or acting in concert.

In conclusion, I will say that preventing disease is one of the most important services of public health policy. The most effective way to prevent disease is to understand the cause and change the conditions that permit it to occur. A key strategy to prevent many diseases will be use of knowledge from gene-environment interaction research to estimate individual risk and then to use this information for design of approaches for better health and treatment.

Finally, our Institute at the NIH (the NIEHS) has also been working with a new model of research that provides for citizen participation. We believe that citizen participation in research will generate more relevant findings, will suggest better "real-world" research questions, and will serve to enhance communication for the participants and their neighborhoods.

Thank you again for this opportunity. I will be happy to answer questions.